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Overall review on analytical method development and validation of Dasatinib

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Abstract

In this review article determines the different analytical methods for the quantitative establishment of Dasatinib by using HPLC, HPLCMS, HPLC-UV, LC-MS/MS. Pharmaceutical analytical method development of Dasatinib requires valid analytical procedures for quantitative and qualitative analysis in Pharmaceuticals dosage formulations and human serum. This assessment explains that the superiority of the HPLC/LC-MS methods reviewed is based on the quantitative analysis of drugs in formulations, (API), biological fluids such as serum and plasma.

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Introduction

Dasatinib, sold under the brand name Sprycel among others, is a targeted therapy medication used to treat certain cases of chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL) [1]. Specifically it is used to treat cases that are Philadelphia chromosome-positive (Ph+). It is taken by mouth.

Common adverse effects include low white blood cells, low blood platelets, anemia, swelling, rash, and diarrhea. Severe adverse effects may include bleeding, pulmonary edema, heart failure, and prolonged QT syndrome. Use during pregnancy may result in harm to the baby [2]. It is a tyrosine-kinase inhibitor and works by blocking a number of tyrosine kinases such as Bcr-Abl and the Src kinase family.

Dasatinib was approved for medical use in the United States and in the European Union in 2006 [3]. It is on the World Health Organization's List of Essential Medicines.

Pharmacology

Dasatinib is an ATP-competitive protein tyrosine kinase inhibitor. The main targets of dasatinib are BCR/Abl (the "Philadelphia chromosome"), Src, c-Kit, ephrin receptors, and several other tyrosine kinases [4]. Strong inhibition of the activated BCR-ABL kinase distinguishes dasatinib from other CML treatments, such as imatinib and nilotinib [5] [6]. Although dasatinib only has a plasma half-life of three to five hours, the strong binding to BCR-ABL1 results in a longer duration of action [7].

History

Dasatinib was developed by collaboration of Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd, and

named for Bristol-Myers Squibb research fellow Jagabandhu Das, whose program leader says that the drug would not have come into existence had he not challenged some of the medicinal chemists' underlying assumptions at a time when progress in the development of the molecule had stalled

Dasatinib has been shown to eliminate senescent cells in cultured adipocyte progenitor cells. Dasatinib has been shown to induce apoptosis in senescent cells by inhibiting Src kinase, whereas quercetin inhibits the anti-apoptotic protein Bcl-xL. Administration of dasatinib along with quercetin to mice improved cardiovascular function and eliminated senescent cells. Aged mice given dasatinib with quercetin showed improved health and survival.

Giving dasatinib and quercetin to mice eliminated senescent cells and caused a long-term resolution of frailty. A study of fourteen human patients with idiopathic pulmonary fibrosis (a disease characterized by increased numbers of senescent cells) given dasatinib and quercetin showed improved physical function and evidence of reduced senescent cells.

Literature Review of Dasatinib

Saili madur et, al reportednew, simple, sensitive, precise, reproducible UV visible spectrophotometric method was developed for the determination of Dasatinib in Tablet dosage form withmethanol. The method is based on the formation of a colorless complex. The UV spectrum of Dasatinib in methanol showed maximum wavelength at 248 nm. Beer's law is valid in the concentration range of 7-35µg/ml. this method was validated for linearity, accuracy, precision, assay, ruggedness and robustness. The method has demonstrated excellent linearity over the range of 7-35µg/ml with the regression equation y = 0.0332x+0.0633 and regression coefficient i.e. r^2= 0.9994moreover, the method was found to be highly sensitive with LOD(1.08µg/ml) and LOQ(3.29µg/ml). Based on the results the proposed method can be successfully applied for the assay of Dasatinib in various tablet dosage forms.

Panchumarthy Ravisankar et al reported cost effective, precise, accurate, simple stability indicating UV-Spectrophotometric method was developed for the determination of Dasatinib in bulk and tablet dosage form. Dasatinib shows highest λmax at 323 nm. Beer's law was found over a concentration range of 2-10 µg/ml with superior correlation coefficient (r2 = 0.999). The Detection limit (DL) & Quantitation limit (QL) were found to be 0.3968 µg/ml and 1.2025 µg/ml respectively. The results of the Dasatinib recovery analysis were found to be 99.9505 ± 0.0002 to 100.0645 ± 0.0002. Percentage assay of Dasatinib tablets (Dasanat) got more than 99.88 %. Dasatinib was subjected to alkali, acid, oxidation, thermal, UV light degradation. Dasatinib is more unstable in acidic, oxidation, thermal and stable in alkaline and ultra violet (UV) light irradiation. The Proposed spectrophotometric method was validated as per the ICH Q1A (R2) guidelines. While estimating the Dasatinib in tablet formulation there was no interference of additives & excipients. Hence this method can safely be employed for the routine quality control analysis of Dasatinib in bulk and tablet dosage form.

Gowri Sankar et al. reports UV spectrophotometric method has been developed for the quantitative estimation of dasatinib in pure form as well as in pharmaceutical formulations. The drug exhibits absorption maximum at 330 nm in 0.1N HCl and obeys Beer's law in the concentration range of 2-10 µg/mL. The method was extended to pharmaceutical preparations and there is no interference from any common pharmaceutical additives.

B. Ramachandra et al reports that a simple, economical, accurate, precise and reproducible UV-Visible spectrophotometric method for the routine estimation of dasatinib has been developed. The method is based on the formation of a bluish green colored complex by dasatinib in presence of MBTH reagent. The developed colored complex showed λmax at 630 nm. Beer's law in the concentration range of 10 to 60 µg/ ml. Results of analysis were authenticated statistically as well as by recovery studies, which gave mean recovery between 99 to 100%. The method was successful in determining dasatinib in pharmaceutical formulation and biological samples, with an average recovery between 99 to 100 % respectively. The proposed method could find application to product development scientists in ongoing research; as well provide an additional tool for routine analysis of dasatinib.

JyotiMittha, et , al reported that UV-Spectrophotometric method has been developed and validated for quantitative estimation of dasatinib in bulk and pharmaceutical formulation. Dasatinib is soluble in acetonitrile, so it was used as solvent. Dasatinib was dissolved in acetonitrile and resulting solution was scanned in UV range (200-400nm). The max was found to be 315nm. Beers law is valid in concentration range of 5-25µg/ml. The developed method was validated for linearity, accuracy, precision, robustness; LOD and LOQ. Linearity was obtained in the range of 5-25µg/ml with correlation coefficient 0.9992. LOD and LOQ were found to be

0.908µg/ml and 2.752µg/ml respectively. The method showed good reproducibility and recovery so; proposed method can be applied for routine analysis of dasatinib in bulk and pharmaceutical formulation.

Somnath Patil et al reported thatThe aim of present work is to develop a simple, accurate, precise, rapid, economical UV Spectrophotometric method for the estimation of Dasatinib in bulk and tablet dosage form. Method: Spiked Dasatinib arrangement was checked over UV- visible extend for its absorbance maxima. Results: The absorbance maximum was determined at 232 nm using 0.1% formic acid as a solvent. The relationship coefficient over the concentration extend of 40-60 µg/ml was found 0.9995. The LOD and LOQ of Dasatinib were found 0.687445 and 2.083166 respectively. The method was successfully applied to Dasatinib in marketed formulation and results were in good agreement with label claims

Alagar Raja M. et al. reported that simple, fast, accurate and precise UV-spectroscopic method and RP-HPLC method were developed and validated for the estimation of per ICH guidelines. The λ max of Dasatinib was found to be 315nm RP-HPLC method was developed by using Triethyl amine buffer solution PH 6.5 ±0.05 and solvent mixture (Methanol, Acetonitrile) in (50:50v/v) was used as the solvent and flow rate was set on 1.1 ml/min at 315 nm, retention time for Dasatinib was found to be 12 min. The method was developed in Cosmicsil BDS C18 column (100 mm × 4.6 mm, 3.5µm particle size). In RP-HPLC method was found to be linear in the range of is Dasatinib 50- 150µg/ml and with a correlation coefficient value of 0.999. The accuracy studies of RP-HPLC method was performed at five different levels, i.e. 50%, 75%, 100%, 125% and 150% and recovery was found to be in the range of 101 to 101.5% for Dasatinib respectively. This method was Rugged and Robust in different testing criteria, The Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be LOD value was 2.83 and LOQ value was 9.41 for RP-HPLC method.

Panchumarthy Ravi Sankar et al reported that objective of the present study was to develop and validate a novel RP-HPLC method for the determination of Dasatinib in the pharmaceutical dosage form. Chromatographic separation was conducted on Agilent technologies-1260 series with the G1311C quaternary pump, Thermo Scientific C_{18} column (4.6 mm i.d. × 250 mm, 5 µm particle size) and equipped with photodiode array detector G1315D. The mobile phase consisted of methanol and acetonitrile mixed in the ratio of 50:50 v/v, was used at a flow rate of 1 ml/min, and the detection wavelength was set at 323 nm. The retention time for Dasatinib was found to be 4.073 min. The calibration was linear (r^2= 0.999) in the concentration range of 2-10 µg/ml. The limit of detection and the limit of quantitation were found to be 0.5263 µg/ml and 1.5948 µg/ml, respectively. Recovery of Dasatinib in tablet formulation was observed in the range of 98.09-99.57%. Percentage assay of Dasatinib (Dasanat) was found to be 99.45% w/w. Thus the novel proposed method for Dasatinib was found to be feasible for the estimation of Dasatinib in bulk as well as the pharmaceutical dosage form.

A. Sreedevi et.al Reported that simple, accurate, precise RP-HPLC method was developed and validated for the estimation of Dasatinib in bulk and pharmaceutical dosage forms. A Hypersil BDS C18 column (150 mm x 4.6 mm), 5 µ particle size was used as stationary phase with mobile phase consisting of phosphate buffer and acetonitrile in the ratio of 85:15 V/V. The flow rate was maintained at 1.1 mL/min and effluents were monitored at 300 nm. The retention time was 3.164 min. The linearity of the method was observed in the concentration range of 25-150 µg/mL with correlation coefficient of 0.999. The percentage assay of Dasatinib was 99.93%. The method was validated for its accuracy, precision and system suitability. The results obtained in the study were within the limits of ICH guidelines and hence this method can be used for the estimation of Dasatinib in pharmaceutical dosage forms.

Bandi Ramachandra et.al reported that A new simple accurate and suitable reverse phase high performance liquid chromatographic method was developed for the determination of Dasatinib in bulk and tablet dosage form. The separation was eluted on a Inertsil C8 column (100 mm x 4.6 mm; 5µ) using a mobile phase mixture of sodium phosphate buffer pH 6.5±0.1 and Methanol in a ratio of 70:30 v/v at a flow rate of 1.0ml/min. The detection was made at 323 nm. The retention times were 5.789±0.1min for Dasatinib. Calibration curve was linear over the concentration range of 5- 30µg/ml for Dasatinib. The propose method was validated as per the ICH guidelines parameters like Linearity, specificity, precision, accuracy, robustness and ruggedness. The method was accurate, precise, specific and rapid found to be suitable for the quantitative analysis of the drug and dosage form

Jayendrasingh P. Bayas et., al reported that accurate, fast, cost effective and robust RP- HPLC chromatographic method was developed and validated by using Quality by Design approach as per the ICH guide-

lines, for Linearity, Accuracy, Interday-Intraday Precision, Specificity and Selectivity, Robustness, Solution stability. The Design of Experiment was carried out by using 3 level factorial designs using design expert software. Change in pH and Mobile Phase concentration is considered for design of experiment. Based on the results obtained from screening of various mobile phase Acetonitrile as to Water having proportion 50:50 at 4 pH and Maximum Wavelength 315nm were selected for the analysis of Dasatinib by employing QbD methodology. The HPLC method is more sensitive, accurate and precise compared to the previously reported method. There was no interference of excipients in the recovery study. The low value of %RSD, molar extinction coefficient (L mol-1 cm-1) suggested that the developed method is sensitive. The proposed high-performance liquid chromatographic method proved to be convenient simple, cost effective and effective for the quality control of Dasatinib.

K.S. Nataraj et.,al reported that novel reverse phase high performance liquid chromatographic method was developed and validated for the determination of Dasatinib monohydrate tablets. The method was found to be simple, precise and accurate. The method involved a mobile phase comprising of trimethylamine buffer (pH 6.5 ± 0.05) and solvent mixture of methanol and Acetonitrile in 50: 50 v/v and a Cosmicsil BDS C18 (4.6 X 250, 5µ) column. The flow rate was maintained at 1.0 ml/min and the detection was done at 315 nm. The retention time was found to be 6.4 mins. The method was found to be linear in the concentration range of 10-30ppm. The analytical method was validated according to ICH guidelines (ICH Q2b). The correlation coefficient (r2) was found to be 0.9996, % recovery was 101.5-101% and %RSD for precision on replicate injection was 0.18 and intermediate precision for intraday precision at Condition-I and II was 0.10, 0.11 and interday precision was 0.13% respectively. The precision study was precise, robust, and repeatable. LOD value was 2.83 and LOQ value was 9.41. The developed method was validated by performing validation parameters like linearity, accuracy, precision, specificity and robustness. The method was found to be reliable for the determination of Dasatinib monohydrate in pharmaceutical dosage forms.

Y. S. R. V. S. Jogarao Et.,al reported that Separation and quantification of Dasatinib and its impurities are done by using an Inertsil ODS-3V, 250 x 4.6 mm, 5µm and the mobile phase consists of two Channels A and B. Channel-A: pH 5.80 phosphate buffer : acetonitrile (90:10 v/v) and Channel-B: acetonitrile : water (90:10 v/v). The flow rate is 1.0 ml/min. The column temperature was maintained at 25°C and sample temperature was maintained at 25°C, injection volume 10 µL and wavelength fixed at 320nm UV-detection. There is no interference of diluent and placebo at Dasatinib and impurities peaks. The elution order and the retention times of impurities and Dasatinib obtained from individual standard preparations and mixed standard preparations are comparable. The limit of detection (LOD) and limit of quantitation (LOQ) for Dasatinib standard 0.147&0.048 µg/mL, impurity-A 0.334&0.110 µg/mL, Impurity-C 0.184&0.061 µg/mL, Impurity-D 0.136&0.045 µg/mL, Impurity-E 0.089&0.029 µg/mL and impurity-F 0.222 & 0.073 µg/mL respectively.The linearity results for Dasatinib and all the impurities in the specified concentration range are found satisfactory, with a correlation coefficient greater than 0.99. Calibration curve was plotted and correlation co-efficient for Dasatinib and its impurities found to be 1.000, 0.9999, 0.9912, 1.000, 0.9932 and 0.9922 respectively.The accuracy studies were shown as % recovery for Dasatinib and its impurities at specification level. The limit of % recovered shown is in the range of 80 and 120% and the results obtained were found to be within the limits. Hence the method was found to be accurate.The method has validated as per ICH guidelines and all the validation parameters are satisfying the ICH Q2 specification acceptance limits

Dara. Varun et.al reported that The present study describes a newly developed, optimized and validated isocratic RP-HPLC method for the separation of two tyrosine kinase inhibitors (Dasatinib-DST and Erlotinib-ERT) with Methyl paraben-MPB as internal standard (IS), in bulk and pharmaceutical formulations with the aid of Chemometrics, multi criteria decision making (MCDM) approach. The separation was achieved by using Phenomenex Enable C18 column (15×4.6 mm id, 5µm particle size) and PDA-UV-detection at 277nm.The range of independent variables used for the optimization were MeOH: 60-70%, pH: 2-2.5 and flow rate:0.3-0.8ml/min. The influence of these independent variables on the output responses: capacity factor of the first peak (k1), resolution (Rs) and separation (a) of the second peak and retention time (tR3) were evaluated. Using this strategy, mathematical model was defined, and response surface were derived for the separation. The coefficients of determination R2 were more than 0.9258 for all the models. The four responses were simultaneously optimized by using Derringer's desirability functions

and MCDM approach. Optimum conditions chosen for assay were MeOH, 0.01mM KH2PO4 (pH 2.5±0.5) adjusted with diluted orthophosphoric acid solution (68.03:31.97v/v) and flow rate of 0.8 mL/min. Peak area ratio of the analyte and internal standard was used for the quantification of pharmaceutical formulation samples. Total chromatographic analysis time per sample was approximately 9.0 min with DST, MPB (IS) and ERT eluting with retention times of 2.7, 3.2, and 6.0 minutes respectively. The optimized assay condition was validated as per ICH guidelines and applied for the quantitative analysis Sprycel-DST tablet and Tarceva -ERT capsule.

Mohammed G Kassem et.al reported that A highly selective, sensitive, and rapid high performance liquid chromatographic (HPLC) method has been developed and validated to quantify dasatinib, a tyrosine kinase inhibitor, in rabbit plasma. Montelukast was used as internal standard (IS). Dasatinib and IS were extracted by deproteinization technique, followed by injection of aliquot of supernatant into chromatographic system. Chromatographic separation was achieved on a reversed phase C18 column with a mobile phase of 0.02M potassium dihydrogen phosphate: methanol (10:90, v/v) pumped at flow rate of 2.0mL/min. The analytes were detected at 340 and 374nm for excitation and emission, respectively. The assay exhibited a linear range of 50.0-3000ng/mL, with a lower detection limit of 15.0ng/mL. The method was statistically validated for linearity, accuracy, precision, selectivity and stability following FDA guidelines. The intra- and inter-assay coefficients of variation did not exceed 13.5% from the nominal concentration. The accuracy of dasatinib was within ±15% of the theoretical value. The assay has been applied successfully in a pharmacokinetic study

D. Vivekananda Reddy et.al reported that A novel isocratic reverse phase liquid chromatographic (RPHPLC) method was developed and validated for the determination of Dasatinib in bulk drug and its pharmaceutical formulation. Chromatographic separation was achieved on a BDS-C18 column (100 mm × 4.6 mm, 5.0 µ). The mobile phase consisted of 10 mM monobasic phosphate buffer and acetonitrile (67:33v/v) at a flow rate of 1.0 mL min-1 and detection was performed at 300 nm using photodiode array (PDA) detector. The drug was subjected to various ICH prescribed stress conditions including hydrolysis (neutral, acid and alkaline), oxidation, photolysis and thermal degradation.

Xu Kang-kang et.al reported that To establish a method for the content determination of dasatinib and related substances in Dasatinib tablets. HPLC method was adopted. Dasatinib and the related substances were separated on Phenomenex Gemini C18; the mobile phase was 0.1 mol·L -1 ammonium acetate buffer-methanol (25∶75) with flow rate at 1.0 mL·min -1. The detection wavelength was 248 nm and the sample size was 20µL.Dasatinib and the related substances were well-separated. The linear range of dasatinib was 20.0～100.0µg·mL (r=0.999 9) with an average recovery of 99.76%(RSD=0.68%).The content of related substance in 3 batches of samples were 0.13%～0.22%.This method is rapid, accurate and reliable, and it is applicable for the quality control of dasatinib.

Maheen et al. reported that objective of the method was to develop a new, simple, rapid, efficient, cost effective and reproducible, stability indicating Ultra performance liquid chromatography method for quantification of Dasatinib and Lenvatinib in pharmaceutical dosage form as per ICH guidelines. Methods: Chromatographic analysis was carried out by using UPLC on a water Acquity C8 column using a mobile phase sodium phosphate buffer (10mm), pH 3.5 methanol [60:40] was selected as good peak symmetry and resolution between peaks was observed. The flow rate of 0.5ml/min was maintained and detection was carried out at 276nm. The method was validated in terms of linearity, accuracy, precision, LOD, LOQ and robustness as per ICH guidelines. Results: The Retention time of DASATANIB and LENVATINIB were found to be 2.355 and 4.460 min respectively. The linearity the correlation coefficient R2 value was found to be 0.991 for DASATANIB and 0.990 for LENVATINIB. The proposed UPLC method was also valid Dasatinib for system suitability, system precision and method precision. The % RSD in the peak area of drug was found to be less than 2%. The limit of detection of DASATANIB and LENVATINIB were found to be 0.72µg/ml µg/mL and 3.19 µg/mL and limit of quantitation were 2.20µg/mL for dasatinib and 9.67 µg/ml respectively, the percentage of recovery of DASATANIB and LENVATINIB were found to be 98.74 and 99.42 respectively. The drugs were degraded in thermal, photolytic, acidic, basic and peroxide conditions. The peaks of degraded products were well resolved from the actual drug. The results obtained prove that the developed method is astability indicating method. Conclusion: The developed RP-HPLC method was simple, rapid, accurate, precise and stability indicating for the dasatinib and lenvatinib in pharmaceutical dosage form.

Sunil V. Lanke et.,al reported that simple and sensitive reverse phase liquid chromatography (RP-HPLC)

method has been developed for the determination of process related impurities of Dasatinib drug substance. Separation was achieved with a Inertsil ODS 3V, (Make: GL Sciences); 150mm x 4.6mm; particle size 5µmcolumn and buffer was prepared by dissolving 1.36g of potassium dihydrogen phosphate and 1.0g of sodium1-octane sulphonic acid into 1000ml water, dissolve and adjust pH 6.0 with dilute potassium hydroxide solution. The flow rate was set 1ml/minute and the column temperature was 50°C. UV detection was performed at 315nm and injection volume 20µL with ambient sample temperature. The method is simple, rapid, and specific. Themethod is suitable for the determination of almost all process related impurities of Dasatinib drug substance. The method is useful for the determination of following impurities. A) KSM-01(Key starting material: 2-Amino-N-(2-chloro-6-methylphenyl) thiazole-5-carboxamide) b) DAS-01(N-(2-Chloro-6-methylphenyl)-2-[(6-chloro-2- methyl-4-pyrimidinyl)amino]-5 thiazole carboxamide) c) Dimer of DAS-01 d) N-Oxide dasatinib e) N-Deshydroxyethyl dasatinib f)Dimer of dasatinib drug substance

Narasimha S. Lakka et,al reported that Dasatinib is a protein kinase inhibitor used for the treatment of chronic myelogenous leukemia and acute lymphoblastic leukemia. Dasatinib along with its six known organic impurities were separated using the reversed-phase high performance liquid chromatography with C_{18} column and mobile phases consisting of gradient mixture of 20 mM potassium phosphate buffer at pH 6.0 with 1-octanesulphonic acid sodium salt (0.1%, w/v), acetonitrile and ultrapure water. This method was successfully tested with liquid chromatography coupled mass-spectrometry to elucidate the chemical structure of newly formed degradation product of Dasatinib which was identified by comparing its retention time and mass-spectra with literature data. Stability-indicating characteristics of developed HPLC method was assessed using stress testing [5 N HCl at 90 °C/1 h, 5 N NaOH at 90 °C/1 h, H_2O at 90 °C/1 h, 30% H_2O_2 (w/w) at 25 °C ± 5 °C/1 h, dry heat at 105 °C/24 h and UV (200 W h m^{-2}) and fluorescent light (1.2 million lux-h)] and was validated as per ICH Q2(R1). For Dasatinib and its six impurities, the quantification limits, linearity and recoveries were found in range of 0.19–0.21 µg/mL, 0.2–3.0 µg mL^{-1} ($R^2 > 0.995$) and 85.5–107.0%, respectively. The developed HPLC method will also suffice the suitability for impurity profiling and assay of Dasatinib in bulk drugs and pharmaceutical formulations.

D. Jeslin et.,al reported that The purpose of this work was to design and establish an analytical method validation of dissolution method for determining the percent Drug Release in Dasatinib Tablets 20mg, 50mg, and 70mg by HPLC. A high performance liquid chromatography system with the capability of isocratic elution, a spectro photometric UV detector, and an auto sampler (Agilent 1260 HPLC or equivalent). Data handling system (EZ Chrome or equivalent). This investigation utilized an ultrasonic bath Sonicator, PCI analytics model 30L500, Zodiac C18150mm x 4.6mm, 3 m. The detection wavelength was set to 320 nm, and the mobile phase was composed of acetonitrile at a ratio of 70:30 (percent v/v) with a flow rate of 1 ml/min. Dasatinib retention time was determined to be 4,989 minutes. Within the 2-30 g/ml concentration range, the calibration was linear (r2 = 0.999). The approach is determined to be specific, exact, robust, linear, and accurate in the range of 10% to 150% of the specified limit, and it is suitable for its intended application

Conclusion

A sensitive and accurate RP-HPLC method, stability-indicating HPLC, HPLC-PDA, HPLC-UV, stability indicating HPTLC and HPLC-MS, was developed for the estimation of Dasatinib, in pharmaceutical dosage forms, human plasma, the above methods was evaluated for Specificity, Linearity, Accuracy, Precision, Ruggedness and Robustness as per ICH&FDA guidelines.

Conflict of Interest

Authors are declared No Conflict of Interest

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Author Contribution

All Authors Contributed equally

Ethical Considerations

Not Applicable

Inform Consent

Not Applicable

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